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EXAMINER	
CRANE, L.	
ART UNIT	**PAPER NUMBER**
1623	7

DATE MAILED: 08/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/483,337	Applicant(s) Kool	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE --3-- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less that thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall ,by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

[X] Responsive to communication(s) filed on -05/16/00 (amdt A & IDS#1) & 05/24/00 (IDS#2)-.

[] This action is **FINAL.**

[] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

[X] Claims —1-63— are pending in the application. Claim(s) -[]- have been cancelled.
Of the above claim(s) —[]— is/are withdrawn from consideration.

[] Claim(s) —[]— is/are allowed.

[] Claims —[]— are rejected.

[] Claim(s) —[]— is/are objected to.

[X] Claims —1-63— are subject to restriction or election requirement.

Application Papers

[X] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[] The proposed drawing correction, filed on -[]- is [] approved [] disapproved.

[] The drawing(s) filed on -[]- is/are objected to by the Examiner.

[] The specification is objected to by the Examiner.

[] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

[] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).

[] All [] Some* [] None of the CERTIFIED copies of the priority documents have been

[] received.

[] received in Application No. (Series Code/Serial Number) -[]-.

[] received in the national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: -[]-.

Attachment(s)

[X] Information Disclosure Statement(s), PTO-1449, Paper No(s). --4&6--

[] Interview Summary, PTO-413

[] Notice of Reference(s) Cited, PTO-892

[] Notice of Informal Patent Application, PTO-152

[X] Notic of Draftsperson's Patent Drawing Review, PTO-948

[X] Other: -SEQ. ID Information Request-.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1623.

The application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §1.821 through §1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given **3 (THREE)** MONTHS from the date of this letter within which to comply with the sequence rules, 37 C.F.R. §1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. §1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. §1.136. In no case may an applicant extend the period for response beyond the SIX MONTH statutory period. Applicant is requested to return a copy of the attached Notice To Comply with the response.

Applicant is referred to pages 9, 33, 35, 45 and 56 and Figures 3, 4, 7, 8, 11-13, 17 and 19.

No claims have been cancelled and no preliminary amendments filed as of the date of the instant Office action. An Information Disclosure Statement (IDS) has been received with all cited references and made of record.

No claims have been cancelled, no new claims have been added, and the disclosure amended as per the preliminary amendment filed May 16, 2000. Two Information Disclosure Statements (IDS) filed May 16 and May 24, 2000 have been received with all cited references and made of record. In light of the improper claim numbering (two claims numbered "16"), and under the authority of 37 C.F.R. §1.126 the claims have been renumbered and now include claims numbered **1-63**.

Claims **1-63** remain in the case.

Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claim **1**, drawn to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, classified in Class 536, subclasses 026.500 and/or 026.600.

II. Claims **2-5, 11 and 16**, drawn to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end and wherein said oligonucleotide is optionally attached to a solid support and wherein said oligonucleotide is optionally hybridized to a complementary oligonucleotide, classified in Class 536, subclass 023.100.

III. Claims **6-10**, drawn to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage (presumably the product of chemical ligation), classified in Class 536, subclass 023.100.

IV. Claims **12**, drawn to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof, classified in Class 536, subclasses 026.700, 026.800, 027.300, 027.700, 027.810, 028.500, and 028.530.

V. Claims **13-15**, drawn to an oligo-RNA/oligo-DNA modified by attachment of a 5'-deoxy-5'-iodonucleoside at its 5'-end and optionally attached to a solid support, classified in Class 536, subclass 023.100.

VI. Claims **17-18**, drawn to oligonucleotides attached to a solid support but otherwise not defined clearly, classified in Class 536, subclass 023.100.

VII. Claims **19-20**, drawn to a process of making an oligonucleotide via synthetic chemical ligation mediated by formation of an oligonucleotide duplex hybrid wherein the template nucleic acid hybridized with two shorter nucleic acids one of which is 5'-terminally modified by a 5'-iodo group and the other modified by a 3'-terminal nucleoside modified by attachment of a S, Se or Te-substituted phosphate and wherein the shorter nucleic acids are optionally further modified by fluoresent-donor and fluoresent-acceptor labels, respectively, classified in Class 536, subclass 025.330.

VIII. Claims **21-30, 38-43, 49, 55 and 61-62** , drawn to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of two probes with the polymorphic oligonucleotide sequence followed by *in situ* chemical ligation of the separate probes to form a single probe, wherein detection is based on a change in fluorescence following the chemical ligation of the linked pair of oligonucleotide probes one of which is equipped with a fluorescent donor and the other of which is

equipped with a fluorescent acceptor, classified in Class 424, subclass undetermined.

IX. Claims **31-37**, drawn to a method for detecting the presence, absence, or fraction of occurrence of one of two different genetic polymorphisms;
wherein the detection process relies on the adjacent, head-to-tail hybridization of two probes with the target oligonucleotide sequence followed by *in situ* chemical ligation of the separate probes to form a single probe;
wherein the probes used are three in number and are i) a mutant polymorphism probe, ii) a wild-type polymorphism probe and iii) a universal probe;
wherein the probe sequences are selected to permit hybridization of the universal probe either upstream or downstream of the polymorphism with the two polymorphism probes sequences selected to hybridize with the remaining portion of the target sequence;
wherein the terminal modifications are selected to permit the adjacent portions of the universal and polymorphism probes to undergo chemical ligation via a 5'-iodo terminus alkylation of a phosphorothioate or equivalent modified phosphate group present at the terminus of the adjacent hybridized probe;
wherein the universal probe is modified by attachment of a fluorescent energy donor group and the polymorphism probes modified by attachment of a fluorescent energy acceptor group;
the first process step being the contacting of all three probes with the target oligonucleotide sequence and thereby causing the chemical ligation of universal and adjacent polymorphism probes;
the second process step being exposure of the reaction mixture to radiation which causes the ligated product to fluoresce; and

the third step in the process being analysis of the fluorescence emission to determine the character of the product or product mixture generated by the first two steps, classified in Class 424, subclass undetermined.

X. Claims **44-48, 50-54 and 56-60**, drawn to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a universal oligonucleotide probe and a polymorphic oligonucleotide probe followed by *in situ* chemical ligation of the separate probes to form a single probe,
wherein detection is based on the presence of a radiolabel present on one or both initially separate probes; and
wherein the polymorphism probe is optionally less than 7 nucleotides in length;
the first process step being contacting the target oligonucleotide sequence with the probes which upon hybridization undergo spontaneous chemical ligation as described above; and the second step is detection of the linked probes, classified in Class 424, subclass undetermined.

XI. Claim **63**, drawn to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a pyrenyl-substituted, universal oligonucleotide probe and a pyrenyl-substituted, polymorphic oligonucleotide probe followed by *in situ* chemical ligation of the separate probes to form a single probe,
wherein the respective 5'- and 3'-termini are modified by the presence of a 5'-iodopyrenyl nucleoside residue and, a pyrenyl nucleoside equivalent or pyrenyl modified nucleoside also modified by a 3'-phosphorothioate or similar modified phosphate residue; and
wherein the first process step is contacting the target oligonucleotide

sequence with the two modified oligonucleotide probes under hybridization conditions; and
following spontaneous chemical ligation of the probes, detection of the ligated oligonucleotide probe by stimulation of the excimer emission characteristic of the adjacent pyrenyl groups, classified in Class 424, subclass(es) indeterminate.

The inventions are distinct, each from the other because of the following reasons:

Inventions **I and II** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to oligonucleotides which may have a 3'-terminal phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituent.

Inventions **I and III** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage.

Inventions **I and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof.

Inventions **I and V** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to an oligo-RNA/oligo-DNA modified by attachment of a 5'-deoxy-5'-iodonucleoside at its 5'-end and optionally attached to a solid support.

Inventions **I and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly.

Inventions **I and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to a process of making an oligonucleotide via synthetic chemical ligation mediated by formation of an oligonucleotide duplex hybrid wherein the template nucleic acid hybridized with two shorter nucleic acids one of which is 5'-terminally modified by a 5'-iodo group and the other modified by a 3'-terminal nucleoside modified by attachment of a S, Se or Te-substituted phosphate and wherein the shorter nucleic acids are optionally further modified by fluoresent-donor and fluoresent-acceptor labels.

Inventions **I and VIII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of two probes with the polymorphic oligonucleotide sequence followed by *in situ* chemical ligation of the separate probes to form a single probe.

Inventions **I and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to a method for detecting the presence, absence, or fraction of occurrence of one of two different genetic polymorphisms.

Inventions **I and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a universal oligonucleotide probe and a polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **I and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to mononucleotides with a phosphoroselenoate or a phosphorotelluroate substituent, and the second invention being directed to a method for detecting a known genetic polymorphism in

DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a universal, pyrenyl substituted, oligonucleotide probe and a pyrenyl substituted, polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **II and III** are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP §806.04(b), third paragraph), and the species are patentably distinct (MPEP §806.04(h)).

In the instant case the intermediate product is deemed to be useful as **a separate probe attachable to a halomethyl styrene solid support** and the inventions are deemed to be patentably distinct because there is nothing on this record to show them to be obvious variants. Should applicant traverse on the grounds that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 USC § 103(a) of the other invention.

Inventions **II and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second

invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof.

Inventions **II and V** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second invention being directed to an oligo-RNA/oligo-DNA modified by attachment of a 5'-deoxy-5'-iodonucleoside at its 5'-end and optionally attached to a solid support.

Inventions **II and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second invention being directed to.an oligonucleotide attached to a solid support but otherwise not defined clearly.

Inventions **II and VII** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process

of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in materially different process such as a probe.

Inventions **II and VIII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second invention being directed to.a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of two probes with the polymorphic oligonucleotide sequence followed by *in situ* chemical ligation.

Inventions **II and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second invention being directed to a method for detecting the presence, absence, or fraction of occurrence of one of two different genetic polymorphisms.

Inventions **II and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or

they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a universal oligonucleotide probe and a polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **II and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant inventions have different functions, the first invention being directed to an oligonucleotide modified by the attachment of a 3'-phosphorothioate, a 3'-phosphoroselenoate or a 3'-phosphorotelluroate substituted nucleotide at its 3'-end, the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a pyrenyl-substituted, universal oligonucleotide probe and a pyrenyl-substituted, polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **III and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for

a phosphodiester linkage, the second invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof.

Inventions **III and V** are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP §806.04(b), third paragraph), and the species are patentably distinct (MPEP §806.04(h)).

In the instant case the intermediate product is deemed to be useful as a separate oligonucleotide probe attachable by alkylation of it 5'-terminus to an amino-substituted solid support and the inventions are deemed to be patentably distinct because there is nothing on this record to show them to be obvious variants. Should applicant traverse on the grounds that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 USC § 103(a) of the other invention.

Inventions **III and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage, the second invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly.

Inventions **VII and III** are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process claimed can be used to make other and materially different product or (2) that the product made can be made by another and materially different process (MPEP §806.05(f)). In the instant case the product can be made by automated oligonucleotide synthesis wherein the non-standard linkage is introduced as a dimer properly protected and phosphoramidite derivatized.

Inventions **III and VIII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage, the second invention being directed to a process of detecting a genetic polymorphism by variations in fluoresence.

Inventions **III and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage, the second invention being directed to a

process of detecting a genetic polymorphism by variations in fluoresence.

Inventions **III and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage, the second invention being directed to a process of detecting a genetic polymorphism by variations in fluoresence.

Inventions **III and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to an oligonucleotide modified by an internal substitution of a phosphoroselenodiester or phosphorotellurodiester for a phosphodiester linkage, the second invention being directed to a process of detecting a genetic polymorphism by eximer radiation of adjacent pyrenyl substituents.

Inventions **IV and V** are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP §806.04(b), third paragraph), and the species are patentably distinct (MPEP §806.04(h)).

In the instant case the intermediate product is deemed to be useful as a reagent for derivatization by 5'alkylation of an amino-substituted solid support to permit subsequent use thereof for the synthesis of oligonucleotides and the inventions are deemed to be patentably distinct because there is nothing on this record to show them to be obvious variants. Should applicant traverse on the grounds that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 USC § 103(a) of the other invention.

Inventions **IV and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof, and the second invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly.

Inventions **IV and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof, and the second invention being

directed to a process of making an oligonucleotide via synthetic chemical ligation mediated by formation of an oligonucleotide duplex.

Inventions **IV and VIII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of two probes with the polymorphic oligonucleotide sequence followed by *in situ* chemical ligation.

Inventions **IV and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof, and the second invention being directed to a method for detecting the presence, absence, or fraction of occurrence of one of two different genetic polymorphisms.

Inventions **IV and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to 5'-deoxy-5'-iodonucleosides and

phosphoramidite derivatives thereof, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a universal oligonucleotide probe and a polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **IV and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the noted inventions have different functions, the first invention being directed to 5'-deoxy-5'-iodonucleosides and phosphoramidite derivatives thereof, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a pyrenyl-substituted, universal oligonucleotide probe and a pyrenyl-substituted, polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **V and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the instant noted inventions have different functions, the first invention being directed to an oligo-RNA/oligo-DNA modified by attachment of a 5'-deoxy-5'-iodonucleoside at its 5'-end and optionally attached to a solid support, and the second invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly.

Inventions **V and VII** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in materially different process such as production of solid support attached oligonucleotides by the alkylation of an amino-derivatized solid support by the 5'-iodo terminus of the product.

Inventions **V and VIII** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in materially different process such as production of solid support attached oligonucleotides by the alkylation of an amino-derivatized solid support by the 5'-iodo terminus of the product.

Inventions **V and IX** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in materially different process such as production of solid

support attached oligonucleotides by the alkylation of an amino-derivatized solid support by the 5'-iodo terminus of the product.

Inventions **V and X** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in materially different process such as production of solid support attached oligonucleotides by the alkylation of an amino-derivatized solid support by the 5'-iodo terminus of the product.

Inventions **V and XI** are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP §806.05(h)). In the instant case the product as claimed can be used in materially different process such as production of solid support attached oligonucleotides by the alkylation of an amino-derivatized solid support by the 5'-iodo terminus of the product.

Inventions **VI and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly, and the second invention being directed

to a process of making an oligonucleotide via synthetic chemical ligation mediated by formation of an oligonucleotide duplex hybrid.

Inventions **VI and VIII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of two probes with the polymorphic oligonucleotide sequence followed by *in situ* chemical ligation.

Inventions **VI and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly, and the second invention being directed to a method for detecting the presence, absence, or fraction of occurrence of one of two different genetic polymorphisms; wherein the detection process relies on the adjacent, head-to-tail hybridization of two probes with the target oligonucleotide sequence followed by *in situ* chemical ligation.

Inventions **VI and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions,

or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a universal oligonucleotide probe and a polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **VI and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to an oligonucleotide attached to a solid support but otherwise not defined clearly, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on the adjacent, head-to-tail hybridization of a pyrenyl-substituted, universal oligonucleotide probe and a pyrenyl-substituted, polymorphic oligonucleotide probe followed by *in situ* chemical ligation.

Inventions **VII and VIII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to a method of linking an oligonucleotide by chemical ligation, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on a donor/acceptor fluorescence effect.

Inventions **VII and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to a method of linking an oligonucleotide by chemical ligation, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on a donor/acceptor fluorescence effect.

Inventions **VII and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to a method of linking an oligonucleotide by chemical ligation, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on a donor/acceptor fluorescence effect.

Inventions **VII and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to a method of linking an oligonucleotide by chemical ligation, and the second invention being directed to a method for detecting a known genetic polymorphism in DNA or RNA wherein the detection relies on an excimer emission induced by irradiation of adjacent pyrenyl substituents.

Inventions **VIII and IX** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the two inventions using different combinations of probes to produce a detectable ligated probe detectable by a donor/acceptor fluorescence effect.

Inventions **VIII and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention relying on a donor/acceptor fluorescence effect, and the second invention relying on the detection of radiolabels.

Inventions **VIII and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention relying on a donor/acceptor fluorescence effect, and the second invention relying on the generation of an excimer emission caused by irradiation of adjacent pyrenyl substituents.

Inventions **IX and X** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the

instant case the inventions have different modes of operation, the first invention relying on a donor/acceptor fluorescence effect, and the second invention relying on the detection of radiolabels.

Inventions **IX and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention relying on a donor/acceptor fluorescence effect, and the second invention relying on the generation of an excimer emission caused by irradiation of adjacent pyrenyl substituents.

Inventions **X and XI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention relying on the detection of radiolabels, and the second invention relying on the generation of an excimer emission caused by irradiation of adjacent pyrenyl substituents.

Because these inventions are distinct for the reasons given above and 1) have acquired a separate status in the art as shown by their different classifications, 2) have acquired a separate status in the art because of their recognized divergent subject matter, and 3) the search required for inventions **I, IV and VII** is not required for inventions **II, III, V-VI and VII-IX**, restriction for examination purposes as indicated is proper.

A telephone call was made to Ms. Victoria A. Sandberg on August 17, 2001 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. §1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor if at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(h).

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines operated by Group 1600 are **(703) 308-4556** and **703-305-3592**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-**308-4639**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Gary Geist, can be reached at (703)-308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is 703-**308-1235**.

LECrane:lec
08/21/01

L. Eric Crane
Patent Examiner
Group 1600